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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,803	05/25/2001	Stephen B. Liggett	MWH-0029US	3706

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GENAISSANCE PHARMACEUTICALS
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NEW HAVEN, CT 06511

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,803	Applicant(s) LIGGETT, STEPHEN B.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *9,10,12,16-21, 23 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed May 27, 2004. Applicants arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This application contains claims 9, 10, 12, 16-21, 23, and 26-29 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Timmermann (Kidney International. June 1998. 53: 1455-1460).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches

detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457).

4. Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Timmermann (Journal of Molecular Medicine (May 1998) 76: B30, Abstract P109).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles.

5. Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Timmermann (Human Mutation (March 1998) 11(4): 343-344).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention.

6. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenzen (WO 97/35973).

Lenzen teaches an oligonucleotide designated therein as SEQ ID NO: 27 which comprises present SEQ ID NO: 5.

SEQ ID NO:27 of Lenzen: 5'- CCGAGGTCCG CCCGCTGAGG-3'

Present SEQ ID NO: 5: 5'- GTCCG CCCGCTGAGG-3'.

It is a property of the oligonucleotide of Lenzen that it is an allele-specific oligonucleotide that specifically hybridizes to a β2-AR polynucleotide region containing the 5' LC polymorphic site.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Kidney International) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is

identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457). Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

However, Green teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the method comprises using allele specific primers to amplify the β2-AR (see for example, page 26). Green teaches that the allele specific primers are designed so that the 3' end nucleotide of the primer is modified so that it is complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it

was well known in the art at the time the invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

8. Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles. Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

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complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it was well known in the art at the time the invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation (March 1998) 11(4): 343-344) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

However, Green teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the method comprises using allele specific primers to amplify the β2-AR (see for example, page 26). Green teaches that the allele specific primers are designed so that the 3' end nucleotide of the primer is modified so that it is complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to

have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it was well known in the art at the time the invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

10. Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Kidney International) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also

teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457). Timmermann does not teach detecting the -47 mutation using allele specific probes.

However, Soppet teaches methods for detecting polymorphisms in adrenergic receptor genes. Soppet (column 15) teaches that polymorphisms may be detected by sequencing or by first amplifying the DNA and detecting the polymorphism using allele specific probes.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific probes as taught by Soppet in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 5 and 6 since the prior art teaches methods for designing probes that are allele specific and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific probes and methods of using said probes for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

11.Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

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the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 5 and 6 since the prior art teaches methods for designing probes that are allele specific and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific probes and methods of using said probes for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach amplifying the target nucleic acids using allele specific primers. Timmermann does not teach detecting the -47 mutation using allele specific probes.

However, Soppet teaches methods for detecting polymorphisms in adrenergic receptor genes. Soppet (column 15) teaches that polymorphisms may be detected by sequencing or by first amplifying the DNA and detecting the polymorphism using allele specific probes.

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13.Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Large (Journal of Clinical Investigation

(1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

However, Large teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the methods comprise amplifying the β2-AR gene and detecting a polymorphism in the gene by RFLP analysis. As taught by Large, the presence of a polymorphism in a gene may introduce or remove a restriction enzyme site. The loss or gain of a restriction enzyme site may be detected by digesting the DNA with the restriction enzyme and separating the DNA by gel electrophoresis to detect a change in the length of a restriction enzyme fragment, relative to a control sample (see, for example, Figure 1). Large teaches that this methodology can be used to distinguish between individuals homozygous and heterozygous for the polymorphic sequence. Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al. Furthermore, the New

England Biolabs teaches the MspA1 I enzyme and the site at which this enzyme cleaves double-stranded DNA.

In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analysis since the sequence surrounding the -47 polymorphism was taught by Emorine and computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

14. Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Large (Journal of Clinical Investigation (1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the

β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

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In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47

5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analysis since the sequence surrounding the -47 polymorphism was taught by Emorine and computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

15. Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Large (Journal of Clinical Investigation (1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

However, Large teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the methods comprise amplifying the β2-AR gene and detecting a polymorphism in the gene by RFLP analysis. As taught by Large, the presence of a polymorphism in a gene may introduce or remove a restriction enzyme site. The loss or gain of a restriction enzyme site may be detected by digesting the DNA with the restriction enzyme and separating the DNA by gel electrophoresis to detect a change in the length of a restriction enzyme fragment, relative to a control sample (see, for example, Figure 1). Large teaches that this methodology can be used to distinguish between individuals homozygous and heterozygous for the polymorphic sequence. Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al. Furthermore, the New England Biolabs teaches the MspA1 I enzyme and the site at which this enzyme cleaves double-stranded DNA.

In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analysis since the sequence surrounding the -47 polymorphism was taught by Emorine and

computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

16. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emorine in view of Soppet and Brooks-Wilson.

The claims are drawn broadly to methods for genotyping the β2-AR gene. As written, the claims include methods which generically determine the sequence of the β2-AR gene. Emorine teaches methods of sequencing the β2-AR gene and teaches the resulting sequence of the β2-AR gene including the leader cistron sequences (see page 6995 and Figure 1). Emorine does not teach determining the sequence of both copies of the β2-AR gene.

However, Brooks-Wilson teaches methods for sequencing genomic DNA and for determining the presence of mutations and polymorphisms in DNA. In the method of Brooks-Wilson, genomic DNA is amplified by PCR, cycle sequencing is performed, and sequences are determined and analyzed for the presence of heterozygous positions (see column 28). The method of Brooks-Wilson results in the analysis of the sequence of both copies of a genomic DNA sequence. Furthermore, Soppet teaches the importance of determining the sequence of adrenergic receptor genes and of identifying sequence variations in the adrenergic receptor genes (see, for example, columns 15-16).

In view of the teachings of Soppet and Brooks-Wilson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the β2-AR gene using the cycle sequencing method of Brooks-Wilson in order to have provided an effective means for analyzing the β2-AR gene for the presence of genetic variation. Such a method would have analyzed all positions of the β2-AR gene including the -47 5' LC polymorphic site and would have necessarily identified the nucleotide pair present at the 5' LC polymorphic site.

RESPONSE TO ARGUMENTS

17. **Rejections under 35 U.S. C. 102(a) and 103 over Timmerman (June, May and March 1998):**

In the response filed May 27, 2004, Applicants state that each of the 102 and 103 rejections over the Timmermann references of June, May and March 1998 has been overcome by the filing of a 1.131 declaration demonstrating that the invention embodied in the claims occurred prior to the effective date of the cited references. The 1.131 declaration has been fully considered but is not sufficient to antedate the Timmermann references. It is noted that the content of the 1.131 declaration is sufficient to establish a date for methods for determining the identity of the nucleotide pair at position –47 of the 5'LC (i.e. the "5' leader polymorphic site") prior to that of the Timmermann references. However, as set forth in MPEP 715, "The 37 CFR 1.131 affidavit or declaration must contain an allegation that the acts relied upon to establish the date prior to the reference or activity were carried out in this country or in a NAFTA country or WTO member

country. See 35 U.S.C. 104." The present 1.131 declaration does not include such a statement.

18. **Rejection of claims 13 and 14 under 35 U.S. C. 102(b) over Lenzen :**

In the response filed May 27, 2004, Applicants state that the rejection over Lenzen has been overcome by the filing of a 1.131 declaration. However, the Lenzen reference was published more than one year prior to the earliest effective filing date of provisional application 60/109,886 (filling date 11/25/98). The Lenzen reference is a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by an affidavit or declaration under 37 CFR 1.131. Further, it is noted that the declaration states that Stephen B. Liggett, M.D. is the "original, sole and first inventor of the subject matter that is claimed in pending claims 1-8 and 11." The declaration does not indicate that Dr. Liggett is the inventor of claims 13 and 14. The declaration also does not address the subject matter of claims 13 and 14, i.e., oligonucleotides of 10-100 nucleotides comprising the 5'LC polymorphism.

19. **Rejection of claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Emorine in view of Soppet and Brooks-Wilson**:

In the response of May 27, 2004, Applicants traversed this rejection by arguing that the combined references do not teach each of the limitations set forth in the claims. It is stated that the Applicant has identified a polymorphism in the 5' leader cistron of the β2-AR gene and that the references do not teach a polymorphism at this position. It is further stated that the claims have been amended to recite that the method is one which detects a nucleotide pair wherein the nucleotide pair is (a) a cytosine or cytosine, (b) a

cytosine and thymine or (c) a thymine and thymine. Applicants state that this step is not taught by the prior art

Applicants arguments and amendment have been fully considered but are not persuasive to overcome the present grounds of rejection. As written, the claims encompass methods which detect only a thymine at position –47 of the 5' LC. Thymine is the nucleotide present in the wild-type sequence of the β2-AR gene taught by Emorine. Accordingly, modification of the method of Emorine so as to have sequenced both alleles of the β2-AR gene as taught by Brooks-Wilson would have necessarily resulted in a method which determines the identity of the "nucleotide pair "at position –47 of the 5' LC wherein the "nucleotide pair" at this position is a thymine and thymine when the β2-AR gene consists of the wild-type sequence. Since the claims as written read on methods of sequencing both alleles of the β2-AR gene, there is no requirement that the prior art teach that a polymorphism exists at position –47 of the 5'LC. The claims do not require the detection of the newly identified variant allele, i.e., the detection of a cytosine at position –47 of the 5'LC. Rather, the claims allow for the analysis of the wild-type gene and the determination that the wild-type gene contains a thymine at position –47 of the 5'LC.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

20. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emorine in view of Soppet.

Emorine teaches an oligonucleotide comprising each of the sequences of SEQ ID NO: 6 and 8. In particular, nucleotides 1210-1224 of the oligonucleotide of Emorine comprise present SEQ ID NO: 6 and nucleotides 1198-1217 of the oligonucleotide of Emorine comprise present SEQ ID NO: 8. The oligonucleotide of Emorine is considered to be an allele specific oligonucleotide because it is fully complementary to and will hybridize specifically to the 5' LC polymorphic site. Emorine does not teach an oligonucleotide limited to a length of 10-100 nucleotides which includes nucleotides 1210-1224 or 1198-1217 of the sequence of Emorine.

Soppet teaches methods for detecting adrenergic receptor genes and methods of determining the sequence and identifying sequence variations in the adrenergic receptor genes (see, for example, columns 15-16). Soppet further teaches primers and probes for detecting and analyzing adrenergic receptor genes wherein the primers and probes are of a length preferably of at least 10 or 20 or 30 or 50 nucleotides (column 5 and 14). The reference also teaches that fragments of adrenergic receptor genes may be used to synthesize of polypeptides which can then be utilized to generate antibodies, wherein the polypeptides may be of a length of about 30 amino acids (columns 5-6 and 17). Further, Soppet teaches oligonucleotide fragments of adrenergic receptor genes of a length of 10-40 nucleotides wherein the oligonucleotides can be screened to identify those oligonucleotides useful for antisense technologies to inhibit expression of adrenergic receptor genes.

In view of the teachings of Soppet, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have obtained fragments of the β2-

AR gene of a length of 10-90 nucleotides, including fragments that comprise the –47 5'LC sequence and fragments that comprise nucleotides 1210-1224 or 1198-1217 of the β2-AR gene sequence of Emorine. One of ordinary skill in the art would have been motivated to have generated such fragments in order to have developed oligonucleotides that could be used as primers or probes to detect the β2-AR gene, or which could be used to encode polypeptides useful for generating antibodies, or which could be screened to identify oligonucleotides useful for antisense technologies. It is noted that the claims are not limited to specific fragments of the β2-AR gene. Rather, the claims encompass oligonucleotides of up to 100 nucleotides that include the –47 5'LC polymorphism or include nucleotides 1210-1224 or 1198-1217 of the sequence of Emorine. The presence of these nucleotides within an oligonucleotide of 100 nucleotides does not impart any particular unexpected property. In the absence of evidence to the contrary, all fragments of the β2-AR gene of 100 nucleotides are considered to be equivalents. Accordingly, the teachings of the combined references would have lead the ordinary artisan to oligonucleotide fragments of the β2-AR gene of up to 100 nucleotides in length, including the broadly claimed oligonucleotides which comprise position –47 of the 5'LC or which comprise nucleotides 1210-1224 of the 5'LC β2-AR gene sequence of Emorine.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Carla Myers
July 27, 2004

CARLA J. MYERS
PRIMARY EXAMINER